

## REMARKS

### I. Amendments to the Specification

The specification has been updated with respect to the cross referencing of related applications. In addition, several minor and inadvertent typographical and grammatical errors have been corrected.

The structures appearing on page 5, line 7, and page 12, line 6, have been amended to remove the extraneous apostrophe adjacent to the hydrogen atom.

The paragraph on page 6, beginning at line 12, has been amended to remove the extra verb "is" in the last sentence.

An oxygen atom has been inserted between the repeating monomeric portion and the adjacent ethylene moiety in the structure provided in the penultimate sentence of the paragraph bridging pages 8 and 9. Support for the amended structure is provided at page 1, line 18. In addition, those of ordinary skill in the art will recognize that the intended structure includes an oxygen atom between the repeating monomeric portion and the adjacent ethylene moiety given the intended representation of a poly(ethylene glycol). In addition, the article --a-- has been added in the last sentence to provide proper syntax.

The paragraph on page 10, beginning at line 6, has been amended to address the incorrect placement of the word --other-- in the first sentence.

The paragraph on page 10, beginning at line 22, has been amended to replace the incorrect singular form of "backbone" with the plural form --backbones--.

The second sentence of the paragraph on page 11, beginning at line 15, has been changed to substitute "proteins" and "peptides" for --a protein-- and --a peptide--, respectively. Given the context of the sentence, the singular forms are indicated.

The paragraph on page 13, beginning at line 28, has been amended to remove the extraneous word "of."

The paragraph on page 15, beginning at line 15, has been changed to replace the word "for" with the words --to the-- in the second sentence in order to address improper syntax. In addition, the verb "is" has been changed to the verb --are-- in order to provide correct agreement between subject and verb.

For the sake of consistency among the exemplary polymers, the small letter "k" has been replaced by the upper case --K-- in the Example on page 16, line 8.

A superfluous end parenthesis mark (")") as well as an extraneous comma (",") have been removed from the first sentence in the paragraph bridging pages 16 and 17.

In the paragraph on page 17, beginning at line 8, a box ("□") erroneously inserted by a word processor has been corrected to a degrees symbol ("°") in the second sentence.

In the paragraph on page 18, beginning at line 22, a box ("□") erroneously inserted by a word processor has been corrected to a degrees symbol ("°"). This correction appears in two instances in this paragraph.

In the paragraph on page 19, beginning at line 20, a box ("□") erroneously inserted by a word processor has been corrected to a degrees symbol ("°") in the first sentence. In addition, the extraneous abbreviation "ml" has been deleted in the first sentence. Moreover, a missing end parenthesis (")") has been added in the first sentence. Finally, the number four ("4") has been corrected to read as a subscript within the chemical formula --MgSO<sub>4</sub>-- in the penultimate sentence.

In the paragraph bridging pages 19 and 20, the number four ("4") has been corrected to read as a subscript within the chemical formula --MgSO<sub>4</sub>-- in the fourth sentence.

In the paragraph on page 20, beginning at line 9, the number four ("4") has been corrected to read as a subscript within the chemical formula --MgSO<sub>4</sub>-- in the third sentence. In addition, two extraneous commas (",") have been removed and two beginning parenthesis mark ("("), and an end parenthesis mark (")") have been added in the penultimate sentence for the sake of clarity and consistency with respect to NMR data.

In the paragraph on page 21, beginning at line 4, the number four ("4") has been corrected to read as a subscript within the chemical formula --MgSO<sub>4</sub>-- in the fourth sentence.

In the paragraph on page 21, beginning at line 17, an extraneous comma (",") has been removed and an beginning parenthesis mark ("("), and an end parenthesis mark (")") have been added in the last sentence for the sake of clarity and consistency with respect to NMR data. In addition, the number two ("2") has been corrected to read as a subscript within the chemical formula --CH<sub>2</sub>CO<sub>2</sub>NS--. Please note that, as stated above, underlined characters represent additions except when the underlined characters are used to refer to the protons corresponding to NMR signals.

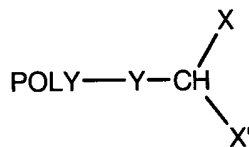
As the changes to the specification merely correct minor and inadvertent typographical errors and/or are otherwise supported by the specification as filed, entry of the changes to the specification is deemed proper.

## II. Amendments to the Claims

Claims 1-53 have been canceled without prejudice. Claims 54-79 have been added. Upon entry of the preliminary amendment, the claims will encompass, among other things, structurally defined polymers.

Support for the new claims is identified below. Additional support other than that identified below may exist in the specification and/or experimental for one or more new claims.

Claim 54. Support for the structure recited in claim 54 is based on the structure appearing on page 5, line 6, as well as page 12, line 6, of the specification. There, the structure



is provided, wherein the specification further provides (on page 5, lines 19-21) that "X and X' are represented by -W-Z and -W'-Z' respectively, in which Z and Z' represent reactive moieties for conjugating the polymer to another molecule [and] W and W' represent tethering groups." As indicated on page 5, lines 8-9, "Poly is a water soluble, substantially non-immunogenic polymer backbone, [and] Y is a hydrolytically stable linkage."

Applicants note that the enumerating modifiers "first" and "second" (as in *first* tethering group, *second* tethering group, *first* reactive moiety, and *second* reactive moiety) recited in claim 54 are supported in the specification in view of the corresponding designations of W (i.e., W naught), W' (W prime), Z (i.e., Z naught), and Z' (i.e., Z primed). As will be recognized by the Examiner, the switch from "naught" and "prime" designations to "first" and "second" designations serves to bring the claim into conformance with standard patent claiming practice.

Claim 55. Support for polymers wherein the first reactive moiety, Z, and the second reactive moiety, Z', are different is found on page 13, lines 13-14, of the specification.

Claim 56. Page 13, lines 13-14, of the specification also supports polymers wherein the first reactive moiety, Z, and the second reactive moiety, Z', are the same.

Claim 57. Support for reciting that the first reactive moiety, Z, and the second reactive moiety, Z', are selected from the group consisting of active esters, active carbonates, aldehydes, isocyanates, epoxides, alcohols, maleimides, vinylsulfones, hydrazides, dithiopyridines, and iodoacetamides is found on page 5, lines 23-26, and page 11, lines 19-22.

Claim 58. Support for reciting that the first reactive moiety, Z, and the second reactive moiety, Z', are each maleimide is found on page 5, line 25, and page 11, line 21. As the structure of maleimide is known to one of ordinary skill in the art, the structural depiction provided in claim 58 is a mere matter of substituting the known structure of a maleimide for each of Z and Z'.

Claim 59. Support for defining that the first tethering group, W, and the second tethering group, W', are each independently selected from the group consisting of alkyl chains, ether chains, amide chains, and combinations thereof is located on page 5, lines 21-23, and the paragraph bridging page 11, of the specification. Support for reciting that the tethering group can also be CH<sub>2</sub> is found at page 20, line 19.

Claim 60. The hydrolytically stable linkages of "-O-", "-S-", and "-CO-NH-" recited in claim 60 are found on page 12, lines 15-16. Support for the remaining hydrolytically stable linkages recited in claim 60, i.e., -O<sub>2</sub>C-NH-, -OCH<sub>2</sub>CH<sub>2</sub>-, -OCH<sub>2</sub>CH<sub>2</sub>CONH-, is premised on the compounds identified below. For each compound, the portion corresponding to the hydrolytically stable linkage, Y, is indicated in **bold**.

Page 16, line 7: mPEG<sub>5K</sub>-**O<sub>2</sub>CNH**-CH(CH<sub>2</sub>CO<sub>2</sub>NS)<sub>2</sub>.

Page 23, line 3: CH<sub>3</sub>-O-PEG<sub>5000</sub>-**O-CH<sub>2</sub>-CH<sub>2</sub>**CH(CO<sub>2</sub>H)<sub>2</sub>.

Page 16, line 17: mPEG<sub>20K</sub>-**OCH<sub>2</sub>CH<sub>2</sub>CONH**CH(CH<sub>2</sub>-O<sub>2</sub>CCH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H)<sub>2</sub>.

Claim 61. Support for the hydrolytically stable linkages "-O<sub>2</sub>C-NH-" and "-C(O)-NH-" is found on page 16, line 7, and page 12, line 16, respectively, of the specification.

Claim 62. Support for defining the water-soluble, substantially non-immunogenic polymer, POLY, as a poly(ethylene glycol) is found on page 8, lines 22-23, page 12, lines 12-14, as well as the examples.

Claim 63. Support for including a capping group in the polymer is found on page 5, lines 15-16, and page 12, lines 21-23.

Claim 64. Linear poly(ethylene glycol)s are found on page 5, line 11, and page 9, line 14, of the specification.

Claim 65. Support for defining the linear poly(ethylene glycol) as  $-\text{CH}_2\text{CH}_2\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-$  is found on page 1, line 23, and the paragraph bridging pages 8 and 9 (as amended) while defining (n) as being from about 8 to 4000 is found on page 9, line 11, of the specification.

Claim 66. Support for poly(ethylene glycol) having a molecular weight of from about 200 to about 100,000 Da is found on page 9, lines 12-13, of the specification.

Claim 67. The structure provided in claim 67 is based on the structure of claim 54, wherein: (i) the water-soluble, substantially non-immunogenic polymer, POLY, is defined as  $-\text{CH}_2\text{CH}_2\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-$  (finding support on page 1, line 23, and the amended paragraph bridging pages 8 and 9) and has a terminal end capping group, "H<sub>3</sub>CO-" (finding support on page 13, lines 17-21); (ii) the hydrolytically stable linkage, Y, is defined as  $-\text{O}-\text{C}(\text{O})-\text{NH}-$  (finding support on page 16, line 7, in structure  $\text{mPEG}_{5K}-\text{O}_2\text{CNH}-\text{CH}(\text{CH}_2\text{CO}_2\text{NS})_2$  wherein the bold atoms represent the corresponding Y linkage); and (iii) the first reactive moiety, Z, and the second reactive moiety, Z', are each maleimide (finding support on page 6, line 27, and page 13, lines 13-14), wherein the structure of maleimide was known to one of ordinary skill in the art at the time the invention was made.

Claim 68. Support for a poly(ethylene glycol) having a molecular weight of about 5,000 Da is found on page 16, lines 7 and 8, and in Example 3.

Claim 69. Support for a poly(ethylene glycol) having a molecular weight of about 20,000 Da is found in Example 2.

Claim 70. The structure provided in claim 70 is based on the structure of claim 54, wherein: (i) the water-soluble, substantially non-immunogenic polymer, POLY, is defined as  $-\text{CH}_2\text{CH}_2\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-$  (finding support on page 1, line 23, and the amended paragraph bridging pages 8 and 9) and has a terminal end capping group, "H<sub>3</sub>CO-" (finding support on page 13, lines 17-21); (ii) the hydrolytically stable linkage, Y, is defined as  $-\text{C}(\text{O})-\text{NH}-$  (finding support on page 12, line 16); and (iii) the first reactive moiety, Z, and the second reactive moiety, Z', are each maleimide (finding support on page 6, line 27, and page 13, lines 13-14),

wherein the structure of maleimide was known to one of ordinary skill in the art at the time the invention was made.

Claim 71. Support for a poly(ethylene glycol) having a molecular weight of about 5,000 Da is found on page 16, lines 7 and 8, and in Example 3.

Claim 72. Support for a poly(ethylene glycol) having a molecular weight of about 20,000 Da is found in Example 2.

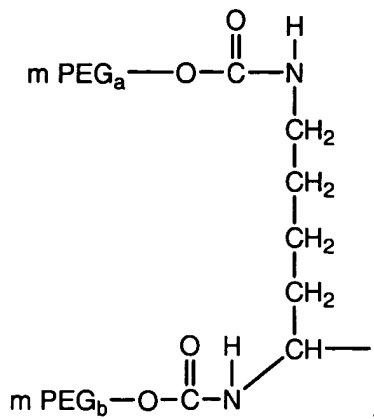
Claim 73. The structure provided in claim 73 is based on the structure of claim 54, wherein: (i) the water-soluble, substantially non-immunogenic polymer, POLY, is defined as " $\text{-CH}_2\text{CH}_2\text{O-(CH}_2\text{CH}_2\text{O)}_n\text{-CH}_2\text{CH}_2\text{-}$ " (finding support on page 1, line 23, and the amended paragraph bridging pages 8 and 9) and has a terminal end capping group, "HO-" (finding support on page 5, line 16); (ii) the hydrolytically stable linkage, Y, is defined as " $\text{-O-C(O)-NH-}$ " (finding support on page 16, line 7, in structure  $\text{mPEG}_{5K}\text{-O}_2\text{CNH-CH(CH}_2\text{CO}_2\text{NS)}_2$  wherein the bold atoms represent the corresponding Y linkage); and (iii) the first reactive moiety, Z, and the second reactive moiety, Z', are each maleimide (finding support on page 6, line 27, and page 13, lines 13-14), wherein the structure of maleimide was known to one of ordinary skill in the art at the time the invention was made.

Claim 74. The structure provided in claim 74 is based on the structure of claim 54, wherein: (i) the water-soluble, substantially non-immunogenic polymer, POLY, is defined as " $\text{-CH}_2\text{CH}_2\text{O-(CH}_2\text{CH}_2\text{O)}_n\text{-CH}_2\text{CH}_2\text{-}$ " (finding support on page 1, line 23, and the amended paragraph bridging pages 8 and 9) and has a terminal end capping group, "HO-" (finding support on page 5, line 16); (ii) the hydrolytically stable linkage, Y, is defined as " $\text{-C(O)-NH-}$ " (finding support on page 12, line 16); and (iii) the first reactive moiety, Z, and the second reactive moiety, Z', are each maleimide (finding support on page 6, line 27, and page 13, lines 13-14), wherein the structure of maleimide was known to one of ordinary skill in the art at the time the invention was made.

Claim 75. Branched poly(ethylene glycol)s are found on page 5, line 11, and page 9, line 14, of the specification.

Claim 76. Support for branched poly(ethylene glycol) being derived from lysine is found on page 9, lines 24-25, of the specification.

Claim 77. Support for the structure provided in claim 75 is based on the structure of claim 54, wherein the water-soluble, substantially non-immunogenic polymer, POLY, is defined as the branched moiety



which finds support from U.S. Patent No. 5,932,462, a patent which is incorporated in the present application by reference. See the present specification at page 10, lines 3-4. A copy of the front page of the U.S. Patent No. 5,932,462 is provided in Appendix A. Substituting "H<sub>3</sub>CO-CH<sub>2</sub>CH<sub>2</sub>O-(CH<sub>2</sub>CH<sub>2</sub>O)<sub>n</sub>-CH<sub>2</sub>CH<sub>2</sub>-" (as explained above with respect to claim 67) for each of mPEG<sub>a</sub> and mPEG<sub>b</sub>, "C(O)-NH-" as the hydrolytically stable linkage, Y (finding support at page 12, line 16), and "maleimide" for each of the first reactive moiety, Z, and the second reactive moiety, Z' (finding support on page 6, line 27, and page 13, lines 13-14), results in the claimed polymer.

Claim 78. Support for a poly(ethylene glycol) having a molecular weight of about 5,000 Da is found on page 16, lines 7 and 8, and in Example 3.

Claim 79. Support for a poly(ethylene glycol) having a molecular weight of about 20,000 Da is found in Example 2.

As support for the claimed subject matter is found in the application as filed, no new matter is introduced by the entry of the above-identified changes to the claims.

### III. Conclusion

In view of the foregoing, Applicants submit that the pending claims satisfy the requirements of patentability and are therefore in condition for allowance. Consequently, a prompt mailing of a Notice of Allowance is earnestly solicited.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 620-5506.

Respectfully submitted,  
Nektar Therapeutics

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